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EPIDEMIC ENCEPHALITIS (ENCEPHALITIS LETHARGICA, NONA).

REPORT OF STUDIES CONDUCTED IN THE UNITED STATES.

By H. F. SMITH, Passed Assistant Surgeon, United States Public Health Service.

Introduction.

Epidemic encephalitis (encephalitis lethargica, nona) may be defined as an epidemic syndrome characterized in most instances by a gradual onset with headache, vertigo, disturbances of vision, ocular palsies, changes in speech, dysphagia, marked asthenia, fever (usually of a low grade), obstinate constipation, incontinence of urine, a peculiar mask-like expression of the face, and a state of lethargy which gradually develops in the majority of the recognized cases into a coma that is more or less profound. Developing with the lethargy and coma there is practically always involvement of the third, fourth, or sixth cranial nerve, either singly or in combination, resulting in ocular palsies and followed in a large number of cases by facial paralysis and paralysis of one or more of the extremities. There are in many of the cases some muscular rigidity of the limbs and the presence of marked tremors, especially during convalescence. In a small per cent of the cases a wakeful delirium prevails instead of the state of coma.

Anatomically there is a more or less diffuse encephalitis most marked in the midbrain and characterized by edema, congestion, and minute hemorrhages.

The disease is to be differentiated from epidemic meningitis, cerebral abscess, tubercular meningitis, brain tumors, cerebral syphilis, the rare forms of poliomyelitis, and the various other forms of coma.

Following the receipt by the Surgeon General of the United States Public Health Service of reports of epidemic encephalitis from various State health officers during the spring of 1919, an officer of the Public Health Service was assigned to the duty of making an epidemiological study of the cases so reported. These cases were widely scattered throughout the United States. As rapidly as possible State health officers who reported cases were called upon and the name and address of the case, together with the name and address of the reporting physician, were secured. Each physician reporting cases was then visited

and a history of the case obtained from him. The patient was visited, with the physician's permission, a careful physical examination was made, and such supplementary data as available were secured from the patient's family. This plan was followed in every case possible, the object being to obtain uniform histories in each. The histories thus secured formed one source of data; a second source of data was furnished by State boards of health that had conducted special studies on the reported cases; a third source was furnished by city health administrations that had likewise conducted such investigations; and a fourth source of data was furnished by several physicians who had made scientific studies of groups of three or more cases coming under their observation either as their private patients or as cases referred to or seen by them in consultation.

The writer wishes to take this opportunity to thank most cordially the following State and city officials and physicians for their courtesy and hearty cooperation in making the data contained herein available:

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The original intention in reference to this work was to make an intensive epidemiological study of the outbreak of epidemic encepha-

litis in the United States. Owing, however, to the limited number of cases and to the extensive territory from which reports of cases were received, the epidemiological data have been found to be largely of a negative character. It was found possible, however, to make intensive clinical studies of numerous cases and to secure and correlate certain data that will, it is believed, be of value to the medical profession in the recognition and diagnosis of similar cases should such occur in the future independently or following local epidemic outbreaks of influenza.

Historical Résumé of Epidemic Encephalitis.

OCCURRENCE IN EUROPE.

The first accounts of epidemics of this morbid condition, to which the terms schlafkrankheit, sleeping sickness, nona, brain influenza, and more recently, lethargic encephalitis and epidemic encephalitis have, more or less aptly or inaptly, been applied, are rather vague, but sufficiently comprehensive to leave no reasonable doubt that they relate to the same morbid condition that made its appearance in epidemic form in the wake of the pandemics of influenza of 1889–90 and 1917–18. Elias Camerarius [1] in 1712 published an account of an epidemic of catarrhal fever at Tübingen, which in a few months had spread widely to many countries and provinces and which presented innumerable changes and forms according to the severity and combination of symptoms. In another account [2] of an epidemic at Tübingen a few years later, Camerarius refers to it as being characterized by somnolence with pronounced brain symptoms, and as being called "Schlafkranckheit." The delirium occurred, he says, "particularly at night with wild, turbulent phantasies." Concerning ptosis as the most striking symptom of oculo-motor disturbance, he says there was made "frequently during the day also complaint of eye affliction, not of inflammation, but of difficulty in opening the eyes." In 1768, Lepecq de la Cloture [3] described a "coma somnolentum" following grippe, while Ozanann, who in 1835 published a history of epidemic diseases, mentioned epidemics of "catarrhal fever" with "soporosité" as having occurred in Germany in 1745, in Lyon in 1800, and in Milan in 1802. A review of the nona literature was published by Longuet [4] in 1892, but unfortunately the volume containing this report was not available for reference in Washington at the time these studies were being made.

In connection with the pandemic of influenza of 1889–90, the complications affecting the nervous system received the first systematic

[1] Elias Camerarius, Kurtze Anmerckungen von ansteckenden Kranckheiten bey Gelegenheit der von vielen verächtlich genannten Kranckheit à la mode, oder Febris catarrhalis etc. Tübingen. 1712, 61 pp.

[2] In Ephemerid. curios. natural., quoted by V. Economo: Wien klin. Wchnschr., 1917, xxx, 581.

[3] Quoted by Bassoe, J. Am. Med. Ass., lxxii, 971, 1919.

[4] Longuet: Sem. med., xii, 275, 1892.

study, including records of cases and descriptions of clinical and necropsy findings. One of the most authoritative and complete reports of this time was that of Leichtenstern,[5] who stated in his introductory remarks that the manifestations on the part of the nervous system are very numerous and varied, but he laid emphasis on the fact that the frequently profound prostration in its intensity and long persistence is out of all proportion to the transient character of the local process and the fever. With respect to the sensorium, he refers to headache as the most constant symptom, at times distributed over the entire head, but more frequently limited to the frontal and orbital regions, at times so severe that the patient assumes a vacant stare (cephalæa attonita), or throws himself about in agony (cephalæa jactatoria s. furibunda). Both at the height of the disease and when convalescence has been established there will frequently develop primarily neuralgias and myalgias, especially of the trigeminus. With respect to motor-nerve complications, he reports the observance of tonic-clonic spasms of the entire body musculature. He gives the clinical histories of 7 cases in which hemiplegia or monoplegia developed. Stupor is noted in only one of these cases. Two of these cases were fatal, but consent to necropsy could not be obtained. The eighth case was characterized by an early-appearing fatal coma. Necropsy revealed slight pachymeningitis hemorrhagica interna of both sides; pia at the base normal; no emboli. Pia over the convexity, clouded intensely and injected, was so adherent that it could not be removed without bringing with it portions of the cortical substance. There was evidence of purulent exudate along the larger pial vessels. Psychic disturbances (stupor, anguish, depression, hallucinations) were marked in 4 cases and persisted for a long time. Emil Kraepelin[6] reports the clinical histories of 11 cases of psychic disturbances appearing after influenza manifestations had subsided, in which apathy, depression, and confusion of ideas were marked.

Among many other reports from Germany, V. Holst records cases of delirium, mania, and melancholia following grippe; Herzog, 2 cases of myelitis; Reye and Münch, cases of paralysis of embolic type; Eichorst, of aphasia, chorea and paralysis of the urinary bladder; Leyden and Ewald, of meningitis and muscular atrophy; Bergmeister, Eversbusch, Sattler, and Uthoff, of paralysis of accommodation; Königstein, Sattler, and Uthoff, of ophthalmoplegia externa; Fleischer, of diplopia; Königstein, retro-bulbar neuritis and atrophy; Hanser, hemeralopia; Holz, paralysis of right cervical sympathetic, convulsions, coma, and neuralgia; Eisenlohr, multiple neuritis; Bernhardt, hysteria; Erlenmeyer, epilepsy; Leyden, delirium and fatal

[5] Leichtenstern: Deutsche med. Wchnschr., xvi, 509, 1890.
[6] Kraepelin: Deutsche med. Wchnschr., xvi, 209, 1890.

coma; Ewald, of various neuralgias; Drasche, of paralysis of all four extremities and acute anterior poliomyelitis; Baumler, syncope, neuritis, and cardiac neuroses.

From France, Huchard reports cardiac symptoms referable to pneumogastric involvement, such as syncope, slowness of pulse, arythmia, intermittance, collapse, angina pectoris, and persistent anorexia; Comby notes convulsions and rachialgia in children; Bilhaut, Jacksonian epilepsy, paraplegia, intense rachialgia, temporary hemiplegia, revived hysteria; Duhomme, revived hysteria after six years; Féréol, pleurodynia without inflammation, and Landry's paralysis; Gaucher, neuralgia, meningitis, and angina pectoris; Joffroy, delirium and mania; Sevestre, meningitis; Lannois, two cases of unilateral deafness from implication of auditory nerve.

In England, Gilbert Smith records a cerebral form of grippe resembling typhoid, and notes the implication of the nervous mechanism of respiration.

In America, Guiteras speaks of a nervous variety of grippe marked by headache, pain in the eyeballs, neuralgias, restlessness, nervous prostration, lassitude, and local sweats, and has noted meningitis following an attack; Dana records mania, encephalitis, facial paralysis, poliomyelitis, neuralgia, and cardiac prostration following the grippe; Kinnicutt, as sequelæ, reports acute and obstinate neuralgias, peripheral neuritis, mental depression with suicidal tendencies, delirium, visual hallucinations, cramps, herpes zoster, and convulsions in children; Starr, suicidal neurasthenia, neuralgias, and multiple neuritis; Wright, uterine pain, false labor pains, urethral pain, and sudden dyspnœa; Draper, cerebrospinal meningitis.[7]

In 1917 V. Economo published a most excellent account of an outbreak of encephalitis lethargica occurring during that year in Vienna.[8] This is one of the first of the numerous recent articles published on this subject. The findings in the cases recorded parallel quite closely the results of the studies conducted in this country. In order that a comparison of the outbreak of 1917 in Vienna and the recent outbreak in the United States may be made, an abstract of V. Economo's article is given herewith.

A series of cases was observed in Vienna in 1917 which corresponded to none of the usual diagnoses but which among themselves presented a certain similarity which lead to the belief that they could be attributed to the same morbid process. These cases ran usually a sluggish course, the first symptom of which began as a rule acutely with headache and malaise, followed by a state of somnolence frequently associated with a lively delirium. The patient could usually

[7] The last part of this epitome of the literature, the unreferenced portion, is taken from Prof. Church's excellent report and analysis of the nervous features of influenza: Chicago Medical Record, I, 418, 1891.

[8] V. Economo: Wien. klin. Woch., XXX, 581, 1917.

be aroused, but when left alone immediately fell back into the somnolent state. The somnolence varied from a simple sleep in some cases to a profound stupor or coma in others. The duration varied from a short period up to a month or more. In the prolonged cases a state of mental weakness was present during convalescence. Meningeal symptoms were never very pronounced, but occasionally a slight stiffness of the neck, percussion sensitiveness over the cranium, sensitiveness to pressure of the eyeballs or, rarely, a pronounced Kernig's sign was observed. Cases were observed which were apyretic while others ran a pyretic course. With the general symptom complex, as a rule, paralytic manifestations were observed both as cranial nerve palsies and as paralyses of the extremities. The ocular muscles particularly were found to be affected. The ptosis varied in intensity. Paralysis of the other ocular muscle nerves occurred as well as other cranial nerve palsies, and paresis of the extremities with reflex disturbances. The impression is gained that in these cases it is merely a question of a different localization of one and the same morbid process, an encephalitis, the number of cases suggesting the idea of an epidemic.

The striking symptom of the disease was the somnolence, sometimes associated with delirium, sometimes not, which varied from light sleep to the most profound coma with or without fever. Delirium was present as a rule. Its presence and intensity were, however, absolutely independent of the depth of the somnolence or the degree of the fever.

Mild meningeal symptoms in addition to the stupor were a part of the clinical picture. These symptoms however were not pronounced.

The spinal fluid was carefully and repeatedly examined in all cases and usually showed increased pressure at the beginning of the disease. This diminished later despite persisting somnolence. The total protein content was below the normal maximum limit. The number of cellular elements were in most cases less than the upper limit for normal, but in two cases there was a distinct increase of the cellular elements. Repeated bacteriological examinations gave negative results. The Wassermann was always negative both from serum and spinal fluid.

A very constant symptom was the eye muscle disturbances, particularly in the distribution of the third cranial nerve; while the most striking symptom of the motor oculi involvement was the bilateral ptosis. Abducens paralysis also occurred, and likewise visual paresis and nystagmus. Other cranial nerve palsies were also observed. Paralytic and irritation manifestations of the extremities were also a part of the symptom complex. In addition to the paralysis of the extremities a characteristic rigor of the extremities was frequently observed as a striking symptom. In addition to the above, ataxic symptoms were also noted.

As to the cause of the disease, V. Economo states that owing to the accumulative appearance of the cases suspicion might rest on a group of organisms. Toxic processes, due to improper nourishment and typhoid, were excluded. The next suspicion was that the condition might be an influenza encephalitis, particularly since Leichenstern and Oppenheim had emphasized the frequent appearance of encephalitis during influenza epidemics. The results of careful examinations of the necropsy material from two cases, and of the examinations of the spinal fluids from others, however, were negative. While there was some grippe in Vienna during 1917, it was to be noted that there was not an epidemic of influenza, nor had any fatal cases of influenza come for necropsy at the Pathological Institute; neither was there any epidemic of poliomyelitis at that time in that vicinity. No two cases came from the same vicinity, and all of the cases, with one exception, had passed the age of childhood.

The microscopical findings showed small-cell infiltration of the vessels of the gray substance of the third ventricle of the region of the nucleus of the motor oculi, around the aqueduct of Sylvius and the floor of the fourth ventricle. This infiltration was primarily limited to the vascular sheaths. No special taxis for the nerve cells was noted in the cord. The white substance of the cerebrum was for the most part free from the morbid process, and only in the vicinity of the cerebral cortex were the vessels of the white substance frequently infiltrated. Only in two locations were extravasations into the perivascular space noted, and there were no hemorrhages into the tissue, which fact was emphasized because the influenza encephalitis was usually hemorrhagic. The meninges were not greatly modified.

From the above the conclusion was drawn that this encephalitis of mildly epidemic appearance, with the characteristic symptom of somnolence and the characteristic histo-pathological findings, is a specific disease *sui generis* and must be caused by a specific living virus which has a specific affinity for the central nervous system.

The disease made its appearance in France during the early part of 1918, but no definite data as to the actual number of cases occurring can be found.

The French literature up to June, 1919, upon epidemic encephalitis was largely confined to the Bull. et mém. Soc. Méd. d. Hôp. de Paris, 1918 and 1919, and included contributions by Chauffard and Bernard, pages 330, 470; Netter, page 384; Sainton, pages 424, 543; Alfred-Khoury, page 455; Marie and Tretiakokk, page 475; Saint-Martin and Lhermitte, page 457.

All of these contributions treated of a peculiar disease, most often febrile, which began with pains in the head, and sometimes vomiting. Somnolence soon appeared and progressively increased, finally

developing into a coma. Somnolence was described as sometimes being associated with delirium and trembling and exceptionally with convulsions. The ocular musculature was almost always affected, and there was noted ptosis, nystagmus, and diplopia. The muscles of the face were frequently affected and facial paralysis was unilateral or bilateral. There were disturbances of speech and deglutition.

The usual signs of meningitis, particularly rigidity of the neck and Kernig's sign, were absent or only slightly pronounced. Lumbar puncture revealed a clear sterile fluid with normal or only slightly increased cellular elements.

The necropsy findings corresponded with those described by V. Economo. Microscopically there was round cell infiltration about the vessels, particularly on a level with the gray matter of the third ventricle, in the region of the nuclei of the third nerve and around the aqueduct of Sylvius.

A distinct outbreak of the disease occurred in Great Britain in the first half of 1918 and was closely studied by representatives of the Local Government Board. The disease was made reportable for a period of one year. The following conclusions were drawn by English observers: [9]

1. That in its essential primary features the disease has a characteristic symptom series of its own.
2. That between this symptom series and that of the rare forms of poliomyelitis, with which alone it can be confused, the clinical differences are more marked than the resemblances.
3. As the result of epidemiological studies it was concluded that epidemic encephalitis was not a form of acute poliomyelitis, and that its presence and epidemic prevalence depended on conditions other than those necessary for the epidemic prevalence of that disease.
4. Both Prof. Marinesco and Dr. McIntosh, as the result of their separate researches, arrive independently at the conclusion that encephalitis lethargica as it appeared in the English outbreak was identical with the illness described by V. Economo in Austria and by Prof. Netter in France, and that it was a disease *sui generis* anatomically and clinically distinct from analogous affections.

During the outbreak referred to in Great Britain, 228 cases had been reported up to June 30, 1918, and additional studies were conducted by Wilson,[10] Hall,[11] and Findlay.[12]

One case of the disease was reported from Algeria by Ardin-Delteil.[13]

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[9] Reports of Societies.—Discussion of Encephalitis Lethargica: Brit. Med. Jour., ii, 488, 1918.
[10] Wilson, S. A. K., Epidemic Encephalitis: Lancet, London, ii, 7, 1918.
[11] Hall, A. J., Epidemic Encephalitis—Analysis of 16 cases: Brit. Med. Jour., ii, 461, 1918.
[12] Findlay, L., Lethargic Encephalitis: Glasgow Medical Journal, XC, 193, 1918.
[13] Ardin-Delteil: Bull. et mém. Soc. med. hôp., de Paris, 1918, pp. 577.

In the American literature will be found abstracts from articles by Netter,[14,17] Sainton,[15] Dragotti,[16] Marinesco,[18] original articles by Bassoe [19] and Tucker,[20] an editorial in the *Journal of the American Medical Association* entitled Encephalitis Lethargica, a New Disease,[21] and an article in the Public Health Reports of the United States Public Health Service entitled Encephalitis Lethargica, a Notifiable Disease in England.[23]

From the foregoing résumé it will be noted that the disease was observed in central Europe about 1712–1715, and in 1745; in Lyon in 1800; in Milan in 1802; and again in Europe following the pandemic of influenza during 1889 and 1890. It reappeared in central Europe during 1917, in France, Great Britain, and Algeria during 1917–18, and in North America during the latter part of 1918 and the early part of 1919.

OCCURRENCE IN THE UNITED STATES.

Number of cases reported from each State, September, 1918, to May, 1919.

Massachusetts	4	*Louisiana	26
Connecticut	1	*Texas	8
New Hampshire	1	*Arkansas	5
Rhode Island	1	Missouri	1
*New York	43	Iowa	1
*Pennsylvania	3	Oklahoma	3
*Virginia	25	*Illinois	88
Tennessee	4	*Ohio	22
North Carolina	5	California	9
*South Carolina	1	*Republic of Mexico	1
Georgia	2		
Alabama	1	Total report	255

(NOTE.—The States with an asterisk (*) are those in which intensive studies were conducted.)

Owing to the limited time and personnel available for these studies it was possible to conduct investigations in only 9 of the 20 States reporting cases. It was deemed advisable to select those places which reported the greatest number of cases and places that could be visited while en route to the more heavily infected districts.

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[14] Netter, A., Lethargic Encephalitis: J. Am. Med. Ass., lxxi, 1520, 1918. Abstract from Paris Med. Jour., viii, 1699, 1918.

[15] Sainton, P., Lethargic Encephalitis: J. Am. Med. Ass., lxxi, 81, 1918. Abstract from Presse Med. viii, 81, 1918.

[16] Dragotti, G., Lethargic Encephalitis, J. Am. Med. Ass., lxxi, 2183, 1918. Abstract from Polyclinico (sez. prat) xxv, 952, 1918.

[17] Netter, A., Lethargic Encephalitis, J. Am. Med. Ass., lxxi, 73, 1918. Abstract from Bull. Acad. de Med. Paris, lxxix, 237, 1918.

[18] Marinesco, G., Lethargic Encephalitis, Pathological Histology, J. Am. Med. Ass., lxxii, 75, 1918. Abstract from Bull. Acad. Med. Paris, lxxx, 411, 1918.

[19] Bassoe, Peter, Epidemic Encephalitis (Nona): J. Am. Med. Ass., lxxii, 971, 1919.

[20] Tucker, B. R., Epidemic Encephalitis Lethargica: J. Am. Med. Ass., lxxii, 1448, 1919.

[21] Editorial—Encephalitis Lethargica, A New Disease: J. Am. Med. Ass., lxxii, 414, 1919.

[22] Public Health Reports: Lethargic Encephalitis—A notifiable disease in England: Public Health Reports, *34*, 314, 1919. Reprint No. 508.

The States of Louisiana, Arkansas, Texas, Illinois, Ohio, Virginia, South Carolina, Pennsylvania (city of Pittsburgh only), and New York, owing to their geographical location and the number of cases reported, were selected as the States in which to conduct the studies that form the basis of this report. Intensive studies of 178 reported cases were made in these States. State morbidity and mortality reports yielded data on 44 additional cases with reference to age, color, and sex, making available data on 222 out of the total of 255 cases reported for the entire United States.

An analysis of the 222 cases investigated or on which data were secured with reference to confirmation of diagnosis, doubtful, excluded, and unconfirmed cases, is shown in Table I. The unconfirmed cases are those from State morbidity and mortality reports on which insufficient data were available.

TABLE I.—*Classification of reported cases.*

State.	Number of cases reported.	Investigated.			Not investigated.	
					Unconfirmed cases.	
		Confirmed.	Doubtful.	Excluded.	State morbidity.	State mortality.
Louisiana	26	15		4	7	
Illinois	88	50	2	15	21	
New York	43	43				
Virginia	25	10		15		
South Carolina	1	1				
Texas	8	8				
Arkansas	5	0		5		
Ohio	22	6				16
Republic of Mexico	1	1				
Pennsylvania	3	3				
Total	222	137	2	39	28	16

Summary of Table I.

Confirmed cases		137
Doubtful cases		2
Excluded cases		39
Unconfirmed cases:		
State morbidity records	28	
State mortality records	16	
		44
Total		222

From the above figures it will be noted that 39, or 22 per cent, of the total 178 cases investigated were excluded.

The diagnosis in the confirmed cases was made on the clinical history and a careful physical examination of the patient, together with the laboratory examination of the blood and spinal fluid.

In the two doubtful cases it was impossible to secure lumbar punctures or blood counts, the patients being convalescent at the time, and the histories of the two cases were too vague for a definite diagnosis.

Among the excluded cases were found cases of epidemic cerebrospinal meningitis, cerebral syphilis, brain abscess, tubercular meningitis, epilepsy, poliomyelitis, apoplexy, hysteria, and, in one instance, acute alcoholism. The 137 confirmed cases and the 44 cases from State morbidity and mortality reports form the basis of the following data from which the conclusions are drawn.

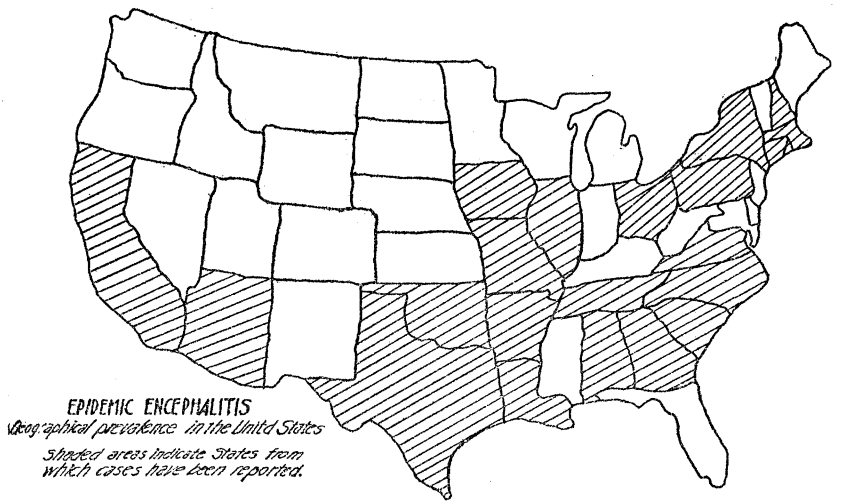

FIG. 1.

Chronological Occurrence of Epidemic Encephalitis in the United States, 1918–19.

The first case of the recent epidemic of encephalitis in the United States on which any data are available occurred in the city of New York on September 4, 1918. The second, third, and fourth cases of the recent outbreak also occurred in New York City on October 4, 15, and 19, respectively. During the month of November one case occurred in Texas on the 2d; two cases in New York on the 6th; two additional cases in New York on the 13th and 21st; one case in Louisiana on the 24th, and one case in Illinois on the 25th. During the month of December six additional cases occurred in the city of New York, two cases in Virginia, and one case each in Ohio and Illinois. During January, 1919, nine cases were reported in New York City, nine cases in Illinois, and one case was reported in Texas. Thirty-five cases were reported during the month of February, and the outbreak reached its peak in March, during which month 61 cases were reported. There was a sharp break in the number of

cases during April, the number being reduced to 12, followed by 5 in May, and no cases were reported for June. Table II and Fig. 2 show the chronological incidence of 153 cases charted by month, and the peak of the epidemic as occurring during March. Table II shows also the geographical distribution of the cases on which Fig. 2 is based.

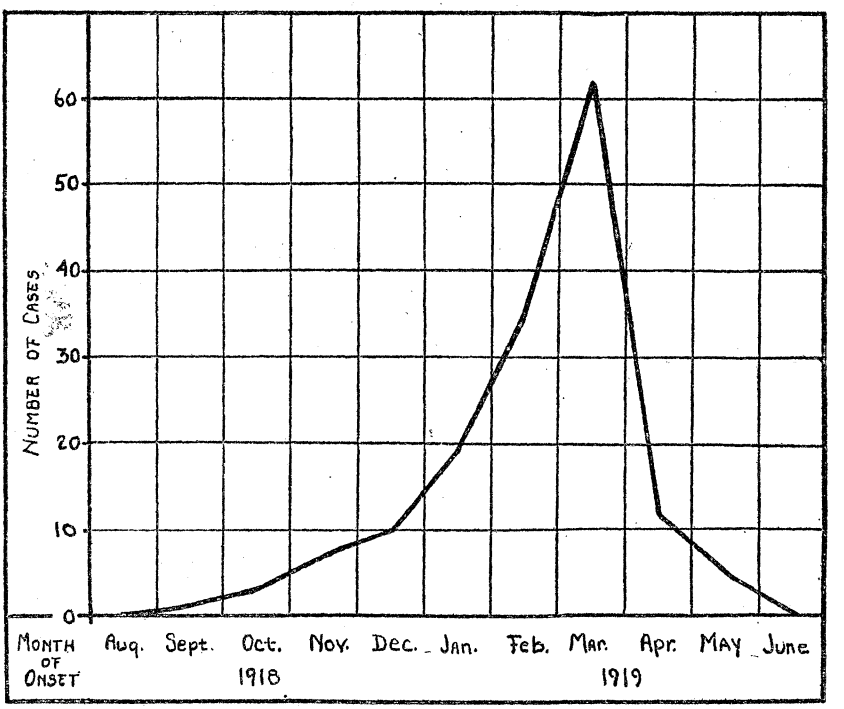

FIG. 2.—Occurrence of epidemic encephalitis in the United States plotted by month of onset.

TABLE II.—*Epidemic encephalitis in the United States during 1918 and 1919, by States and by month of onset.*

State.	Number of cases by months.										
	1918				1919						Total.
	September.	October.	November.	December.	January.	February.	March.	April.	May.	June.	
New York	1	3	4	6	9	8	7	2	2	0	42
Illinois	.....	.....	1	1	9	18	26	7	3	0	65
Louisiana	.....	.....	1	.....	.....	2	17	1	.....	.....	21
Texas	.....	.....	1	.....	1	2	3	1	.....	.....	8
Virginia	.....	.....	.....	2	.....	4	3	.....	.....	.....	9
Ohio	.....	.....	.....	1	.....	1	1	.....	.....	.....	3
Pennsylvania	.....	.....	.....	.....	.....	.....	3	.....	.....	.....	3
South Carolina	.....	.....	.....	.....	.....	.....	1	.....	.....	.....	1
Republic of Mexico	.....	.....	.....	.....	.....	.....	.....	1	.....	.....	1
Total	1	3	7	10	19	35	61	12	5	0	153

While the number of cases is not large, it is interesting to note that the peak of the outbreak in New York City was reached during the month of January; in Virginia during the month of February; and in Louisiana, Illinois, and Texas during the month of March. The largest number of cases for California for any one month (9 in number but not included in Fig. 2 owing to the fact that definite data as to the date of onset could not be secured) were reported in the month of April, which, taken in conjunction with the foregoing in relation to other States, shows a gradual extension of the disease from East to West.

Age Distribution.

The age distribution of the 181 cases on which data were available is shown in Table III.

TABLE III.—*Age distribution 181 cases epidemic encephalitis in the United States.*

Age group (years).	Number of cases.	Per cent of total.
Under 1	6	3.32
1 to 4	21	11.6
Total under 5	27	14.92
5 to 9	22	12.15
10 to 14	15	8.3
15 to 19	12	6.63
20 to 24	15	8.3
25 to 29	13	7.18
30 to 34	14	7.73
35 to 39	12	6.63
40 to 44	20	11.05
45 to 49	8	4.42
50 to 54	7	3.87
55 to 59	6	3.31
60 to 64	5	2.75
65 to 69	4	2.21
70 to 74	.....	.....
75 and over	1	.55
Total, 5 and over	181	100.00

Comparative Age Distribution of Epidemic Encephalitis and Influenza.

The marked difference in the age distribution of the cases of epidemic encephalitis and poliomyelitis is shown in Table IV and Fig. 3.

TABLE IV.—*Comparative age distribution of epidemic encephalitis and poliomyelitis.*

Age group (years).	Number of cases.		Per cent of total.	
	Epidemic encephalitis.	Poliomyelitis.	Epidemic encephalitis.	Poliomyelitis.
Under 1	6	480	3.32	8.63
1 to 4	21	3,308	11.6	59.46
Total under 5	27	3,788	14.92	68.09
5 to 9	22	1,162	12.15	20.9
10 to 14	15	279	8.3	5.01
15 to 19	12	133	6.63	2.4
20 and over	105	201	58.00	3.60
Total	181	5,563	100	100

In Table IV the age distribution of the cases of epidemic encephalitis is based on the 181 cases shown in Table III, while the data in reference to the age distribution of poliomyelitis was taken from 5,563 cases of that disease occurring in the northeastern United States during the epidemic of 1916.[23]

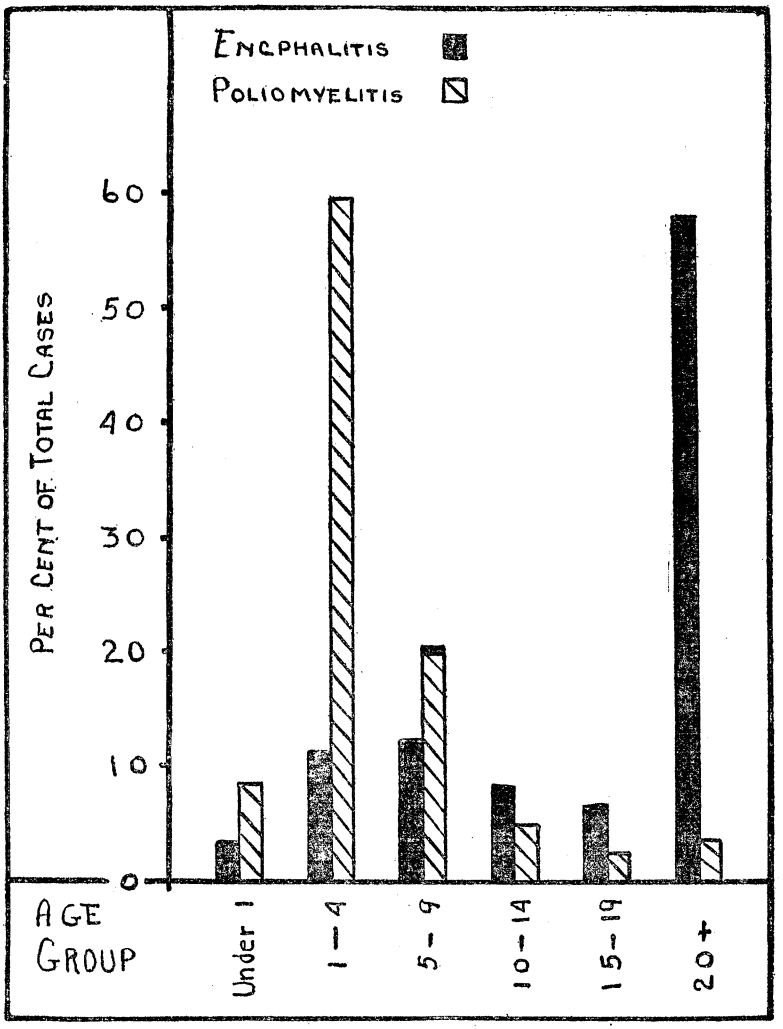

FIG. 3.—Comparative age distribution of epidemic encephalitis and poliomyelitis.

Comparative Age Distribution of Epidemic Encephalitis and Influenza.

Comparison of the age distribution of epidemic encephalitis with the age distribution of influenza shows considerable difference in the percentage of the total cases as distributed in the various age groups.

[23] Lavinder, Freeman, and Frost: Epidemiologic Studies of Poliomyelitis in New York City and Northeastern United States during the year 1916. Public Health Bulletin No. 91.

TABLE V.—*Percentage of population and percentage of cases of epidemic encephalitis and influenza in the various age groups, and the ratio of the percentage of the cases to the percentage of the population in various age groups.*

Age group (years).	Number of cases.		Per cent of population of United States.	Per cent of cases.		Ratio of percentage of cases to percentage of population.	
	Epdemic encephalitis.	Influenza.		Epidemic encephalitis.	Influenza.	Epidemic encephalitis.	Influenza.
Under 10	49	3,085	22.2	27.1	24.2	122	109
10 to 19	27	2,980	19.8	14.9	23.2	75	117
20 to 29	28	2,501	18.7	15.5	19.5	83	104
30 to 39	26	2,092	14.6	14.3	16.3	98	112
40 to 49	28	1,136	10.6	15.5	8.8	146	83
50 to 59	13	589	7.2	7.2	4.7	100	65
60 and over	10	654	6.9	5.5	3.3	80	48

Table V shows the ratio of the percentage of cases of epidemic encephalitis and influenza to the percentage of the total population of the United States in the various age groups. If the distribution of the cases of epidemic encephalitis and influenza in each age group were in direct proportion to the distribution of population in those groups, without showing any particular predilection for any certain age group, then the ratio of the percentage of cases of each disease to the percentage of population in the corresponding age group would be 100.

This, however, is clearly demonstrated not to be the case in either the ratio of the diseases to the population or the ratio of the percentages of the cases in various age groups to each other, and is graphically shown in Fig. 4.

In Table V and Fig. 4 it will be noted that the ratios of the percentage of cases of both epidemic encephalitis and influenza to the percentage of population are relatively high in the age group under 10 years.

In epidemic encephalitis the percentage of the cases in the age group 10 to 39 years is below the percentage of the total population in these age periods, whereas in influenza the percentage of the cases is above the percentage of the population in these age groups.

For the age periods between 40 and 59 years the relative percentage of epidemic encephalitis and influenza to the percentage of the population is reversed, as the ratio of the percentage of the cases of epidemic encephalitis in this age group is above the percentage of the population, whereas the percentage of influenza is below.

In the age group of 60 years and over, the percentage of both epidemic encephalitis and influenza are below the percentage of the population; but in relation to each other the percentage of epidemic encephalitis is considerably higher.

Summary.—Both encephalitis and influenza show a slight predilection for the age group under 10 years. The age group from 10 to 39

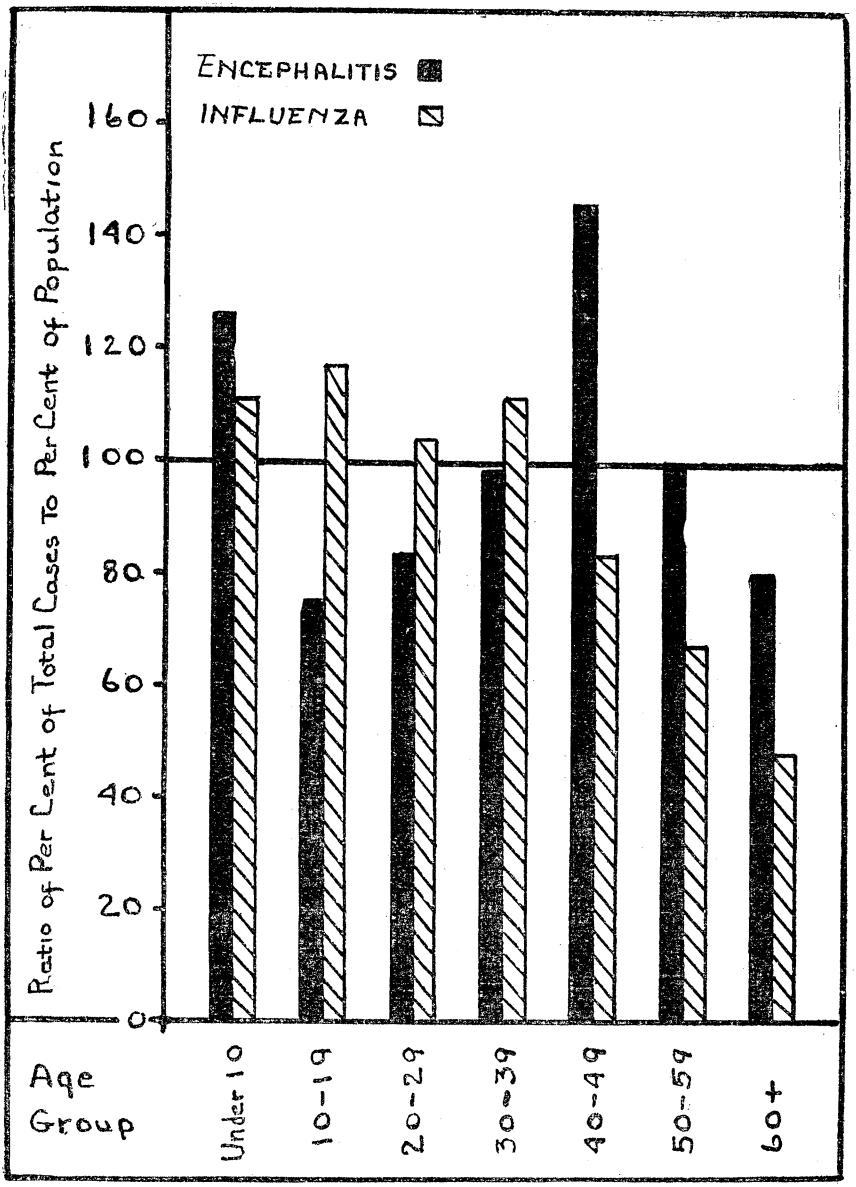

FIG. 1.—Ratio of the percentage of total cases of epidemic encephalitis and of influenza to the percentage of population in various age groups.

years is apparently the least susceptible to epidemic encephalitis but the most susceptible of all to influenza. A further analysis of this age group shows the subgroup 10 to 19 years as the lowest of all periods for epidemic encephalitis and the highest of all 10-year periods for influenza.

The age group from 40 to 59 years shows the highest incidence of any age group for epidemic encephalitis, whereas the incidence of influenza in this group is apparently below the average.

Epidemiological Relation of Epidemic Encephalitis and Influenza.

Reference has previously been made to the article by Elias Camerarius, written in 1715, in which he describes a "schlafkranckheit" and refers to it as being associated with an epidemic of catarrhal fever, which in a few months had spread to many countries.

In 1768 Lepecq de la Cloture described a "coma somnolatum" following grippe.

Ozanann in 1835 mentions epidemics of catarrhal fever with "soporosité" as having occurred in 1745, 1800, and in 1802.

In 1918 in France and England cases of epidemic encephalitis followed in the wake of the pandemic of influenza. Late in 1918 and early in 1919 the disease appeared in the United States following the appearance of influenza in this country. With the exception of the outbreak reported by V. Economo in Vienna in 1917 no record of any outbreak of epidemic encephalitis has been found that was not closely preceded by the epidemic or pandemic appearance of influenza.

While no definite mention of such a disease as epidemic encephalitis is made in the American literature as following the epidemic of influenza in the United States in 1890, nevertheless the mention by Guiteras of cases of influenza characterized by extreme nervousness, marked lassitude, and prostration, by Dana of encephalitis, facial paralysis, and mania, and by Kinnicutt of delirium, visual hallucinations, mental depression, etc., leads one to suspect at least that epidemic encephalitis may have been present during and following the outbreak of influenza referred to in the United States.

With only 255 cases of epidemic encephalitis reported in the United States following the severe epidemic of influenza of 1918–19 it can readily be understood that the probably smaller number of cases which may have occurred following the less severe epidemic of 1890 may have been overlooked in the reporting as such.

In making the epidemiological studies of influenza in the United States, the percentage of the population attacked was found to vary in different communities from 15 per cent in Louisville to 53.3 per cent in San Antonio. It was estimated that the aggregate attack

rate was about 28 per cent.[24] These figures were taken from reports secured mostly in December after the first wave of the epidemic had subsided but before the second wave of the epidemic occurred. Were it possible to secure the attack rate of the second wave and add this to the first, the attack rate would probably reach 30 per cent.

If x equals the percentage of the total population of the United States attacked by influenza, it is only natural to expect a like proportion of x per cent of persons having epidemic encephalitis to give a history of having had a preceding attack of influenza. On this hypothesis it would be expected that at least 30 per cent of the cases studied would give such a history.

In studying the cases of epidemic encephalitis in the United States, efforts were made in all instances possible to secure definite data as to whether or not the patient had had a preceding attack of influenza. All cases in which intelligent data could not be secured on this subject were excluded from this classification of the cases.

Definite data on this subject were secured in 122 cases, the results of which are shown in Table VI.

TABLE VI.—*Classification by sex of 122 cases in reference to preceding attack of influenza.*

	Total number.	With preceding attack of influenza.		No preceding attack of influenza.	
		Number.	Per cent.	Number.	Per cent.
Both sexes....	122	56	46	66	54
Males.....	73	40	55	33	45
Females.....	49	16	32.6	33	67.4

From this table it will be noted that 46 per cent of the cases give a definite history of influenza, which is considerably higher than the per cent of the general population attacked by that disease in the epidemic of 1918–19. While no definite data can be furnished to substantiate the supposition that influenza leaves those having had that disease more susceptible to any malady making its appearance closely following it, the fact should be borne in mind that among the 28 or 30 millions of persons convalescent from influenza, there might have been some who were left with a generally lowered vitality, resistance, or immunity, who might have been more susceptible when exposed to the infection of epidemic encephalitis than would have been the case had the preceding attack of influenza not occurred.

[24] Frost, W. H., The Epidemiology of Influenza: Public Health Reports, 34, 33, Aug. 15, 1919, pp. 1823–1836. Reprint No. 550.

TABLE VII.—*Ratio of males to females in cases having a preceding attack of influenza and the ratio of males to females in cases where no influenza preceded.*

	Number of cases.	Males.		Females.		Ratio of males to females.
		Number of cases.	Per cent of total.	Number of cases.	Per cent of total.	
With influenza preceding....	56	40	71	16	29	2.5 to 1
No influenza preceding.....	66	33	50	33	50	1 to 1

Table VII classifies by sex the cases with and without influenza preceding. Recent studies conducted by the United States Public Health Service show that the attack rates of influenza for males and females in the United States are about equal, approximately 30 per cent. The above table shows, however, that there is considerable difference in the percentage of the males and females having epidemic encephalitis, who gave a previous history of influenza. Among the general population it would be approximately 30 per cent for each of the sexes, whereas among the cases of epidemic encephalitis having a preceding attack of influenza, 40, or 71 per cent, were males and only 16, or 29 per cent, were females. Among those not having a preceding attack of influenza the cases were equally divided among the two sexes.

Mode of Onset.

Definite data on this subject were secured in 122 cases. Of this number, 87, or 71 per cent, gave a history of a gradual onset, while in 35, or 29 per cent of the cases the onset was of a sudden nature. The figures are given in Table VIII. This coincides quite closely with the findings of A. J. Hall [25] in his studies of cases in England, in which 69 per cent were of gradual onset, while 31 per cent were of sudden onset.

TABLE VIII.—*Classification of cases as to type of onset.*

Total number of cases.	Type of onset.			
	Gradual.		Sudden.	
	Number of cases.	Per cent of total.	Number of cases.	Per cent of total.
122	87	71	35	29

The relation of the mode of onset to the prognosis of the case is of interest, owing to the fact that a further analysis of the type of onset

[25] Hall, A. J., Epidemic Encephalitis: Brit. Med. J., ii, 461, 1918.

in relation to the final outcome of the case shows that the mortality among those with a sudden onset is almost three times as great as it is among those cases in which the onset was gradual.

TABLE IX.—*Case fatality rate in cases having a sudden onset and in cases in which the onset was gradual.*

Type of onset.	Number of cases.	Number of deaths.	Case fatality rate.
Gradual.....	87	21	22
Sudden.....	35	21	60

From the table it will be noted that the mortality rate among those having a gradual onset was 22 per cent, whereas the rate among those cases in which the onset was sudden was 60 per cent.

SYMPTOMATOLOGY.

It must be borne in mind that the sources of data in reference to the cases forming these studies were varied. It was impossible to secure complete data on all subjects in all cases. Instances in which the data were lacking, or were of such a vague and indefinite nature as to be unreliable, have been excluded from the compilation of the figures for that particular symptom group.

In the following discussion and in Fig. 5, in reference to the frequency of occurrence of the various symptoms noted, the figures are based only on those cases in which definite data as to the prevalence or absence of the particular symptoms under discussion could be established. In this discussion the subject of symptomatology has been divided into two general groups:

(*a*) Those classified as general symptoms;

(*b*) those symptoms relating to or attributable to disturbances of the central nervous system.

GROUP (A).

1. *Headache.*—Headache, which was found to be one of the earliest and one of the most frequent symptoms, was present in 87 per cent of the cases in which definite data were available. The location varied, but the majority of the cases gave a history of the frontal type.

2. *Lassitude.*—A positive history of lassitude as one of the prodromal symptoms was given in 84 per cent of the cases furnishing data on this subject It varied in intensity but in most cases was a prominent symptom.

3. *Fever.*—Fever was the most constant of all symptoms. In character it was, as a rule, of a light grade, although in two of the cases the temperature reached 106.5° just prior to death. Two of

the cases ran an apyretic course. So far as could be learned, 98.5 per cent of the cases ran temperatures which, as a rule, varied from 100° to 101° or 102°.

4. *Asthenia.*—Asthenia was present in 93 per cent of the cases in which data on same could be secured, and an acute debilitation which was out of proportion to the temperature and relative severity of the other symptoms was one of the striking characteristics of the cases.

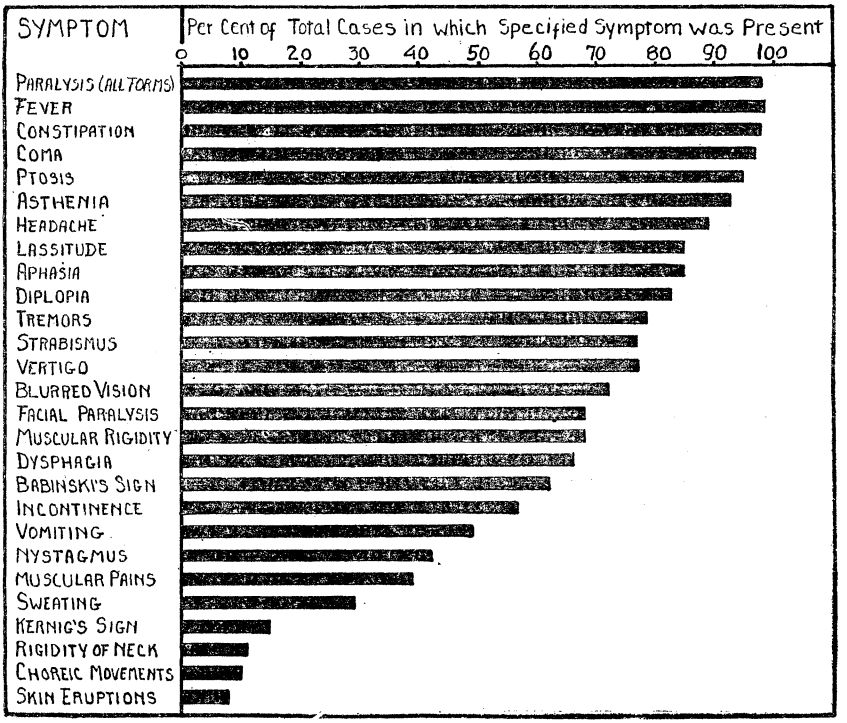

FIG. 5.—Frequency of occurrence of clinical symptoms in epidemic encephalitis.

5. *Vomiting.*—A history of vomiting was positive in 49 per cent of the cases where reliable information was furnished. The incidence of this symptom among those under 20 years of age was slightly higher than in the adult group. Fifty per cent of the occurrences were among those under 20 years of age, whereas the per cent of the total cases was only 42 for the corresponding age group.

6. *Constipation.*—Constipation, obstinate in character, was found in all but one case.

7. *Diarrhea.*—Diarrhea was absent in all cases.

8. *Skin eruptions.*—Skin eruptions were found in 8 per cent of the cases where reliable information was available. These skin

manifestations consisted of small macular eruptions which lasted from one to three days and then entirely disappeared.

9. *Sweating.*—Sweating was present in 29 per cent of the cases and in three instances was quite profuse.

10. *Vertigo.*—Vertigo was present in 77 per cent of the cases and varied in its severity.

11. *Muscular pains.*—Muscular pains were noted in 39 per cent of the cases in which data relating to this subject were available. In some instances considerable muscular pain was present continuously even while the patient remained quiet in bed and was exaggerated on motion; in other cases pain was only present upon active motion.

12. *Urinary disturbances.*—Retention of urine was noted in 9 cases. This was usually in the early course of the disease. Some of these same cases later developed an incontinence of urine. Incontinence was noted in 56 per cent of the cases in which reliable data were obtainable.

GROUP (B).

Symptoms attributable to disturbances of the central nervous system have been divided for this discussion into three subject groups; namely, motor, mental, and meningitic.

One of the most characteristic groups of symptoms of epidemic encephalitis, and one which was noted by even the earliest writers on the subject, was that group showing involvement of the ocular musculature, involvement of the III, IV, and VI cranial nerves, either singly or in combination involving either one or both sides. It is in all probability the most constant symptom, aside from the fever and coma, that one observes in the disease.

The results of the involvement of the III, IV, and VI nerves in this discussion have been classified under six symptoms, namely, blurred vision, diplopia, strabismus, nystagmus, ptosis, and pupillary disturbances.

1. *Blurred vision.*—Blurred vision was among the earliest of the symptoms noted in the individual cases forming the basis of this report, and was present in 72 per cent of the cases studied and on which information of a reliable nature could be obtained. The usual history was of a difficulty in reading or of the general field of vision appearing smoky or hazy. In all cases except four the blurring of the vision was followed by a definite history of diplopia. Of these four cases, one recovered without further eye disturbances, one became temporarily blind, and of the other two no definite history of double vision could be secured. Eighty-six per cent of the instances in which the symptom of blurred vision was noted occurred in persons giving a history of a gradual onset and was usually preceded by headache of a more or less marked degree.

2. *Diplopia.*—Diplopia was present in 83 per cent of the cases on which data were secured.

3. *Strabismus.*—Strabismus was found to be present in 77 per cent of the cases furnishing reliable information on this subject. As to the character of the strabismus definite data were secured on 55 per cent of the cases presenting this symptom. In 85 per cent of these cases the strabismus was of the divergent type and in 15 per cent it was of the convergent type.

4. *Nystagmus.*—Nystagmus was present in 41 per cent of the cases furnishing data on this subject.

5. *Ptosis.*—Ptosis was observed in 95 per cent of the cases affording opportunity in which to note its presence or absence. In intensity it varied from what at times appeared to be merely a physiological heaviness of the lids, which would be expected to be associated with the accompanying lethargy and stupor and which could be overcome by a definite effort on the part of the patient, to a complete paralytic ptosis and an absolute inability on the part of the patient to open the lids even when aroused. In type it was generally bilateral, but several instances in which it was only unilateral were observed.

6. *Pupillary disturbances.*—Opportunity was offered to examine 53 cases for data in regard to the pupillary reflexes. Of this number, 23 showed a normal pupillary reaction on both right and left sides. The reflexes were slightly diminished or sluggish bilaterally in 18 cases. Complete bilateral loss of the pupillary reflexes with fixation of the pupil was present in 11 cases. One case showed a fixation of the pupil on the right side and an accompanying sluggishness of the pupil on the left. It must be borne in mind, however, that these examinations were, in the majority of instances, made but once, and the stage of the disease at the time of the examination would have a certain bearing on the findings.

7. *Facial paralysis.*—Involvement of the VII cranial nerve was noted in 68 per cent of the 63 cases furnishing definite data on this subject. Of the 44 cases showing a definite facial paralysis, 19 presented a right unilateral involvement and 8 a left unilateral, while in the remaining 17, or 39 per cent, the paralysis was bilateral.

A. J. Hall [26] in the analysis of his group of cases in Great Britain reports involvement of the VII nerve in 10, or 62 per cent, of the 16 cases studied. These figures coincide with the results of observations made in this country, as stated above. As the result of this facial paralysis, especially when of the bilateral type, there is a smoothing away of the normal creases and lines of the face, the face assuming a peculiar lack of expression often described as being "masklike."

[26] Hall, A. J., Epidemic Encephalitis—Analysis of 16 cases: Brit. Med. J., ii, 461, 1918.

8. *Paralysis of the muscles of the neck.*—Eight instances were observed in which there was a definite unilateral paralysis of the neck muscles. In six of these cases the paralysis was of the muscles of the right side, accompanied by a more or less marked degree of retraction of the head to the left. Owing to the relaxed condition of many of the patients and to the state of coma, it was difficult to determine the presence or absence of paralysis of the neck muscles, especially when this paralysis was of the bilateral type.

9. *Paralysis of the extremities.*—Definite data in reference to the presence or absence of paralysis involving the extremities were obtained in 83 cases. Of these, 36 per cent showed definite paralysis of one or more of the limbs. This varied in character from a muscular weakness to complete paralysis with the total abolition of the reflexes. A few cases of spastic character were observed, but the great majority of the paralyses were of the flaccid type. Two cases showed a spastic paralysis of the lower and a flaccid paralysis of the upper extremities.

Paralysis of one type or another involving one or more parts of the body was noted in 98 per cent of the cases on which reliable data in reference to this subject were obtainable.

Data were available in reference to superficial abdominal and lumbar reflexes as follows:

Abdominal reflexes were absent in 55 per cent of the cases observed and were frequently unilateral.

Lumber reflexes were absent in 53 per cent of the cases observed and were also at times unilateral.

Tremors.—Dependable information was secured in 47 instances as to the presence or absence of this particular symptom. Thirty-seven, or 79 per cent of these gave a positive history. In the majority of cases these tremors were exaggerated on volitional movements, and were found more frequently during convalescence. Choreic movements were present in 20, or 50 per cent of the cases furnishing data in reference to this symptom. Muscular rigidity was found to be present in 68 per cent of the cases whose history furnished data on this subject. The time of its presence in relation to the course of the disease was found to be in the latter half and during early convalescence.

Aphasia.—Changes in speech were found to be present in 85 per cent of the cases observed and varied from a slight stammering to complete loss of function.

Dysphagia.—Dysphagia was present in 66 per cent of the cases furnishing data and varied in intensity from a slight disturbance to such a marked degree as to necessitate the use of a tube for feeding.

Tendon reflexes.—The results of an examination conducted in reference to the tendon reflexes of the upper and lower extremities of the cases observed is shown in Table X.

TABLE X.—*Results of examination of reflexes of the upper and lower extremities.*

UPPER EXTREMITIES.

Reflexes.	Number of cases on which data were available.	Results.							
		Right.				Left.			
		Normal.	Increased.	Diminished.	Absent.	Normal.	Increased.	Diminished.	Absent.
Biceps	44	15	14	4	11	14	14	5	11
Triceps	40	11	12	4	13	9	13	5	13
Extensors	39	14	12	4	9	12	14	5	8
LOWER EXTREMITIES.									
Patellar	98	27	35	9	27	26	34	8	30
Extensors	42	12	15	5	10	6	18	6	12
Achilles	44	15	14	4	11	9	18	5	12

Table X expressed in percentages.

UPPER EXTREMITIES.

RIGHT.

	Normal.	Increased.	Diminished.	Absent.	Normal or increased.	Diminished or absent.
	Per cent.	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*
Biceps	34	32	9	25	66	34
Triceps	27	30	10	33	57	43
Extensors	36	31	10	23	67	33
LEFT.						
Triceps	32	32	11	25	64	36
Biceps	22	33	12	33	55	45
Extensors	31	36	13	20	67	33

LOWER EXTREMITIES.

RIGHT.

Patella	27.5	36	9	27.5	63.5	36.5
Extensors	29	35	12	24	64	36
Achilles	34	32	9	25	66	33
LEFT.						
Patella	27	35	8	30	62	38
Extensors	14	43	14	29	57	43
Achilles	20	41	11	28	61	39

Laboratory Findings in Spinal Fluid and Blood Examinations.

Two of the most important procedures in the diagnosis of epidemic encephalitis are the laboratory examinations of the spinal fluid and the blood. Lumbar puncture was done in 95 of the cases forming the basis of this report. Owing to the fact, however, that in many of the instances the lumbar puncture was performed on cases in rural districts and at distances from laboratories, which rendered reliable examinations in reference to cultures impossible, complete data on all spinal fluids could not be secured.

Such data as was available is presented in Table XI.

TABLE XI.—*Summary of spinal fluid examinations.*

Examined for—	Number.	Per cent.
Pressure or amount (50 specimens):		
Normal	32	64
Slight increase	18	36
Marked increase	0	0
Appearance (50 specimens):		
Normal	50	100
Cloudy, bloody, etc	0	0
Organisms (38 specimens):		
Present	0	0
Absent	38	100
Protein substances (29 specimens):		
Normal	13	45
Slight increase	16	55
Marked increase	0	0
Wassermann (35 specimens):		
Negative	34	97
Slightly positive	1	3
Positive	0	0
Reduction of Fehling's solutions (43 specimens):		
Normal	43	100
Diminished reduction	0	0
Cytology (45 specimens):		
Normal	16	35
Slight increase	17	38
Moderate increase	8	18
Large increase	4	9

Although from the findings shown in Table XI it will be noted that an examination of the spinal fluid fails to reveal any specific data on which a diagnosis of epidemic encephalitis can be definitely made, positive evidence of a reaction of the meninges due to an inflammation of the brain tissue is found in the increased cells or protein substance or both.

Of more value, however, is the examination as a means of excluding other morbid processes which have been frequently diagnosed and reported as epidemic encephalitis. In one instance the writer investigated 5 cases in two days in which lumbar puncture had not been done but which had been reported as cases of epidemic encephalitis. Lumbar puncture done at the time of the investigation showed in each case a fluid under considerable pressure and of marked turbidity, the presence of coagulum on standing and of varying amounts of pus cells, and Gram-negative diplococci when stained and examined microscopically.

By the normal reduction of Fehling's solution and the failure to demonstrate the tubercle bacillus either by smear or animal inoculation, tuberculous meningitis, one of the most difficult differential diagnoses to make from mild cases of epidemic encephalitis on the clinical findings alone, can be eliminated almost to a certainty.

Cerebrospinal syphilis and epidemic meningitis can be readily excluded by respective examination of the spinal fluid for the same.

In view of the value of the data furnished by the laboratory examination of the spinal fluid in ruling out other diseases it is unquestionably advisable for the diagnostician to give his patient the benefit of such an examination in all cases diagnosed as epidemic encephalitis on clinical grounds.

BLOOD EXAMINATIONS.

Absolute white cell counts were done on 43 cases with the following results:

Under 6,000	1
6,000 to 8,000	12
8,100 to 10,000	9
10,100 to 11,000	3
11,100 to 12,000	4
12,100 to 13,000	1
13,100 to 14,000	4
14,100 to 15,000	4
Over 15,000	5

Combining the above classifications it is shown that 22, or 51 per cent, of the cases gave an absolute count of less than 10,000, and in 21, or 49 per cent, of the cases the absolute count was over this number. In four of the cases in which the absolute count surpassed 10,000, the patients showed at the time definite cases of bronchitis, cystitis, and, in one case, pneumonia, which might readily be accountable for the leucocytosis.

Blood culture was done in four cases with negative results in each.

URINARY ANALYSIS.

The results of the urinary analysis in 50 cases were as follows:

	Present.		Absent.	
	Number of cases.	Per cent.	Number of cases.	Per cent.
Albumin	8	16	42	84
Sugar	1	2	49	98
Casts	3	6	47	94

Census of Families in Which Cases of Epidemic Encephalitis Occurred.

The census of families in which cases of epidemic encephalitis occurred was secured in 58 instances. The total number of persons comprising these families was 226, of which 110 were adults and 116 children. Males and females were about equally distributed.

Basing the census of the average family on 5 persons, the total number of persons exposed for the 181 cases under observation would have been approximately 900. Among this total of persons immediately exposed to known cases of epidemic encephalitis no secondary cases occurred. Efforts were made in every case possible to secure data relative to mild or abortive cases of the disease having been present among other members of the family. The results were always negative.

Case Fatality Rate.

Attention is directed to Table I, which shows that 22 of the total of 181 cases were reported from the State of Ohio. These cases are from the State mortality reports. There were no reports for other cases from this State than those which proved fatal. As these 22 fatal cases comprise 33 per cent of the total deaths occurring without furnishing data in reference to other cases which may have occurred and recovered, they have been deducted from both the morbidity and mortality figures in computing the case fatality rate for the cases observed.

After the deduction of these cases for the above reasons, it was found that 46 deaths occurred in the remaining 159 cases, giving a case fatality rate of 29 per cent.

Animal Inoculation.

The difficulty in securing brain material from fatal cases limited animal experimentation. The following experimental work, however, was conducted at the Hygienic Laboratory of the United States Public Health Service.

Experiment No. 1.—On August 16, *rhesus* monkey No. 1 inoculated intracerebrally through trephine opening with 1 c. c. brain emulsion in salt solution from fatal case of epidemic encephalitis occurring in New York City on February 21, 1919.

Experiment No. 2.—On August 16, *rhesus* monkey No. 2 was inoculated intracerebrally through trephine opening with 0.5 c. c. of brain emulsion in salt solution from fatal case of epidemic encephalitis occurring in New York City on February 21, 1919.

The material used in both of the above inoculations had been preserved in sterile 50 per cent glycerin from February 21 to August 14, 1919.

In both instances the animals recovered without showing any signs of the disease, or, in fact, any ill effects whatever from the procedure.

V. Wiesner claims to have produced the disease in the monkey by subdural infection of 0.2 c. c. of a sedimented brain-cord emulsion from one of V. Economo's fatal cases.[27]

The following is a translation of V. Wiesner's article in reference to his experiments:

"Through the publications of V. Economo our attention was drawn to accumulated cases of a peculiar disease, which he calls encephalitis lethargica; encephalitis, because the post-mortem examination of two typical cases revealed gross and minute changes in the medulla oblongata and cerebrum, corresponding to an acute encephalitis; lethargica, because, in addition to different and alternating cerebral and meningeal clinical manifestations, somnolence or 'sleeping sickness,' increasing from a simple apathy to the most profound coma, existed as a characteristic symptom common to all cases. V. Economo in his publications cites similar observations from the older literature and refers in particular to the accumulated cases of such somnolent states during large influenza epidemics and to the 'sleeping sickness' appearing in the nineties of the last century in northern Italy, known as nona,[28] concerning the etiology of which, so far as the literature of that period reveals, nothing reliable is known.

"The assumption that with the encephalitis lethargica appearing endemically in Vienna and vicinity we are dealing with an infectious disease, hardly requires any supportive argument. In favor of such a view speaks the feverish onset, and in particular the accumulation of cases since February of this year. Since all diseases which may occasionally develop an encephalitis as a secondary manifestation or complication, such as articular rheumatism, typhoid, scarlet fever, measles, diphtheria, influenza, glanders, rabies, or endocarditis, could be positively excluded, another heretofore unknown, uniform infection of possibly specific character with localization of the virus in the central nervous system must be suspected. Aside from the pronounced histological changes in the medulla oblongata and the gray substance of the cerebrum, the localization of the virus in the central nervous system appeared probable from the post-mortem examination of the thoracic and abdominal viscera, since this examination revealed no pronounced organic lesions, aside from purely degenerative changes in the heart muscle and in the parenchyma of the liver and kidneys, which will not be further considered here.

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[27] V. Wiesner, Richard R., The Etiology of Encephalitis Lethargica: Wien. klin. Wchnschr., XXX, No. 30, 933, 1917.

[28] TRANSLATOR'S NOTE.—This statement of V. Wiesner is slightly inaccurate, since V. Economo expressly states that he was unable to find anything concerning nona in the Italian literature except reference to Epstein's quotations from the writings of Camerarius (1712) in *Ephemerid. curios. natural.*—W. D. CANNON

"For the study of the etiology of the disease in question, I made use of the brain and medulla oblongata as working material for both cultural and animal experiments and obtained concordant results with the two methods. In reversing the chronological order of my investigations it was established, that through the inoculation of a monkey (*Macacus rhesus*) with the brain-cord emulsion, a disease clinically similar to encephalitis lethargica of man can be produced.

"Monkey I (*Macacus rhesus*). June 3, 1917, 11 a. m.; trepanation of left parietal bone; subdural injection of about 0.2 cc. of a sedimented brain-cord emulsion of case R. W. (of V. Economo).

"Immediately after the inoculation the animal was normally lively, and climbed about the cage without any apparent disturbances. In the afternoon the animal had already become remarkably quiet, and sat mostly on the floor of the cage.

"On the morning of June 4 the animal moped in a corner of the cage, was somnolent, usually kept its eyes closed, but reacted to call, opened its eyes and screeched. Took food, but chewed with difficulty. Left to itself, the animal immediately drops off to sleep, keeps its eyes closed, and sleeps continuously. The animal continues to relapse into sleep when disturbed, and presents the typical picture of an individual 'fighting sleep.' No stiffness in the neck, slight paresis of the right hind paw, and difficult gait. Tendon reflexes intact. Pupil reaction intact, but sluggish.

"In the afternoon apathy and somnolence considerably increased. The animal supports itself with the forepaws on the crossbars of the cage and, with head resting on them, sleeps. The gait is difficult, slightly ataxic. Paralysis of deglutition. Head inclined toward the right side, but no pronounced rigidity of the neck.

"June 5, a. m.: Complete apathy; animal lies mostly, with eyes closed, on the floor of the cage and no longer responds to call; death 46 hours after inoculation.

"Necropsy of the brain revealed, in short, the well-known picture of acute hemorrhagic encephalitis of the severest form, with particular involvement of the gray substance of the cerebral cortex and of the stem ganglia of both sides, and hyperemia of the delicate membranes of the cerebrum and spinal cord. Incidentally it may be remarked that case R. W., from which the material used for the inoculation was obtained, did not present macroscopically the picture of a hemorrhagic encephalitis. With this experiment the possibility of experimental transmission of encephalitis lethargica of man to monkeys appears to be established, as well as the infectious nature of the disease. That the changes in the central nervous system are possibly not due to the introduction of a toxic substance, but rather to the inoculation of a self-propagating virus, is shown by an inoculation experiment on a second monkey, which was subdurally injected with the filtrate (Berkefeld filter) of the same brain-emulsion, and which showed absolutely no trace of reaction.

"As causal agent of the encephalitis, I was able to isolate culturally from all of the cases that have come to necropsy, and from the brain of the first positively reacting monkey a Gram-positive coccus, which is shown as a round of oval monodiplococcus or as short streptococcus, and which, according to its morphological and biological properties, corresponds neither to a typical diplococcus nor to a typical streptococcus; in respect to its intermediate position between these two types it should be designated as a diplostreptococcus. Concerning its morphology it is to be noted that a certain polymorphism exists, the cocci in the tissue and in the culture appearing as long-ovals, among which are monococci resembling short, plump, bulging rods, and that the inclination to chain formation varies greatly, and the chains frequently are joined, particularly in the fluid culture—that is to say, appear to be composed of joined series of cocci pairs. Of importance also is the fact of pronounced inclination of the cocci to degeneration in the tissue, the globular distension, and the uneven staining property, although not completely decolorized by Gram. In tissue sections the cocci are deposited within the leptomeninges, particularly in the edematously loosened and cellular infiltrated arachnoidal meshes. Their distribution over the surface of the brain is very uneven and the number of cocci relatively small, so that their demonstration is difficult; at times the cocci appear quickly to decompose in the tissue. In the characteristic inflammatory foci in the medulla oblongata and the brain itself I have not thus far been able to demonstrate cocci either in man or in the infected monkey.

"That the cultural demonstration of the cocci was not easily possible is explained by the fact that for the first passage they apparently require anaerobic conditions for their growth. In all cases thus far studied as well as with the infected monkey, cultural demonstration was possible when large pieces of brain surface or medulla oblongata or a corresponding amount of pulp made therefrom were first placed in broth, sugar broth, or in overlayed glucose-agar tubes and after 24 hours transferred to agar plates, whereas the direct planting of small amounts of pulp upon plain agar, sugar-agar, glycerin-agar, or serumagar plates was without any results whatever. The first agar generations sometimes grow very thinly, so that they can hardly be seen with the naked eye. With continued cultivation, however, soon a good growth is obtained under artificial cultural conditions. For obtaining a growth, the addition of glucose to the nutrient media is recommended.

"With respect to cultural behavior, concerning which I shall report in detail in another place, I will note that the agar smear culture resembles in general diplococcus colonies; the colonies, small, delicate, round, usually with smooth border, are slightly green with trans-

mitted light. In broth, very delicate, usually diffuse, sometimes finely-floccular growth; sometimes the broth is left clear, with a trace of sediment. Luxuriant growth with abundant sediment in glucose broth. No hemolysis. Milk usually coagulated with acid formation after 48 hours, sometimes later. Strong acid production in litmus whey, lactose-agar, saccharose and maltose agar; no acid formation from mannite agar. No clearing of the broth with sodium taurocholate and no dissolution of the cocci. Upon glycerin and serum-containing agar no difference of growth as compared with ordinary agar.

"I repeated the inoculation experiment with a pure culture in a long-tailed monkey (*Circopithecus subaeus*). The result of the inoculation was that a few hours after the infection the animal sickened under the symptoms of pronounced apathy, muscular weakness, and somnolence, without, however, showing the severe clinical picture of the first monkey. This condition persisted unchanged for 12 days, after which time the animal was sacrificed. In general the clinical picture was very similar to that of the first monkey. In this case also the animal reacted promptly when called but soon relapsed into somnolence. But there were no cranial nerve symptoms. The necropsy findings were correspondingly mild and were limited to hemorrhages in the medulla oblongata.

"Primarily the medulla oblongata and then the cerebrum must be regarded as the localization of choice of the pathological changes in encephalitis lethargica. However, this does not exclude other localization of changes in the central nervous system, for I have recently observed several cases, in which the changes extended to the spinal cord down to the lumbar region and also to the cerebellum. Without wishing to influence the clinical side of the morbid picture in question, I would like, from an anatomo-pathological standpoint and in respect to the pronounced endemic character, to designate the disease as 'meningoencephalomyelitis,' in which the symptoms-complex of the infection with the diplostreptococcus is not, in my opinion, limited to the cerebral manifestations.

"In support of this view I will point to some anatomical observations and to the results of my studies from the standpoint of etiology and animal experiment. At about the same time when the first cases of encephalitis occurred, my attention was drawn to the frequent appearance of hemorrhagic diatheses at necropsy, associated with simple hemorrhages in the subcutaneous fatty tissue and between the muscle sheaths of the abdominal wall and on the extensor surface of the thigh. It was noted that the corium was not involved, so that such hemorrhages caused no reddening of the skin, at most only a bluish tint, by which they are differentiated chiefly from hem-

orrhages such as occur in morbus maculosus werlhofii, in septic hemorrhages, or in the different forms of purpura. In addition were found petechial hemorrhages in the serous membranes, more rarely in the lung parenchyma and in the intestinal mucosa. The frequency of such findings and the unusual appearance prompted me to undertake cultural experiments with the blood transfusion through enrichment methods, in which large pieces of tissue were planted in broth, sugar broth, and glucose-agar shake culture with the result that in all cases the presence of diplostreptococci could be demonstrated, which morphologically and biologically showed the same behavior as the cocci in meningoencephalomyelitis. In tissue sections the cocci were demonstrable morphologically in the hemorrhages, although usually very sparingly.

"For identification of the cocci the animal experiment was employed, from which the following is recorded. The brain emulsion from case R. W., encephalitis lethargica, which had produced the characteristic symptoms and pathological lesions of encephalitis hemorrhagica in the monkey inoculated subdurally, was introduced intraperitoneally in a rabbit. About 20 hours after the injection the animal was found dead. Necropsy showed somewhat cloudy, serous fluid in the peritoneal cavity, fresh hemorrhages in the parietal peritoneum, over the large intestine, the urinary bladder, and the right cornu of the uterus, hemorrhages in the mucosa of the large intestine, sero-hemorrhagic effusion of the retro-peritoneal tissues of the Douglas space and of the mediastinal tissue, as well as fresh hemorrhages in the parenchyma of the right lower lobe. Culturally the peritoneal exudate and heart's blood showed the diplostreptococci.

"The same inoculation material (brain emulsion) caused in the monkey an encephalitis, in the rabbit a peritonitis with pronounced hemorrhagic diathesis. From these two animals the same diplostreptococcus was recovered in pure culture, which corresponds with the strains isolated from cases of hemorrhagic diatheses. I wish to add, that so far I have observed twice in man at necropsy the combination of meningoencephalitis and hemorrhagic diathesis, and that in monkey I inoculated with brain emulsion of case R. W., hemorrhages in the subcutaneous cellular tissue were observed; hence it appears to me that the chain of evidence of the etiological identity of the two morbid processes is complete.

"The results of my investigations point to the existence of an infectious disease of endemic (frequently epidemic) character caused by a diplococcus. The symptoms-complex and pathological changes of this disease accord with the encephalitis lethargica of V. Economo and include also a pronounced inclination to hemorrhagic diatheses of characteristic anatomo-pathological picture."

In relation to these experiments, however, the following comment by S. A. K. Wilson [29] is certainly to be borne in mind:

"Attention, however, must be for a moment directed to one of the Viennese cases.

"V. Economo's case 10 was that of a girl of 14, whose illness lasted about a month, with fairly characteristic symptoms, and who died on the day of her admission to the clinic. There is no record of a blood or fluid examination. V. Economo states specifically that the pathological appearances were those of polioencephalitis but not of hemorrhagic type. With due aseptic precautions an emulsion of the brain and cord was injected subdurally into a *Macacus rhesus* by Von Wiesner. The animal died in 46 hours, having presented the symptoms of profound stupor for at least 24 hours previously, and with a paresis of the right hind limb. On examination its brain showed all the characteristic appearances of acute hemorrhagic encephalitis, and from it Von Wiesner recovered a Gram-positive diplostreptococcus which he was able to cultivate and from a bouillon culture of which, injection into other apes produced somnolence and muscle weakness, while peritoneal injection in guinea pigs caused death from internal hemorrhage. It is important to note that a filtrate from the original brain-cord emulsion of the patient (Berkefeld filter) injected into a Macaque monkey produced no symptoms. Von Wiesner argues, therefore, that the cause of the disease is this actual bacterial virus, this diplostreptococcus found in the leptomeninges and in cellular infiltrates in the cortex of the first experimental monkey.

"Obviously such results are of much interest and importance; equally obviously they call for confirmation. In this connection one or two points suggest themselves by way of criticism.

"(1) It is curious there is no mention of this organism in the tissues of the patient from whom the emulsion was made.

"(2) It is conceivable that the brain-cord emulsion contained some [quite] other specific virus and that the diplostreptococcus was accidental. That the emulsion filtrate proved negative does not invalidate this criticism altogether, for only one animal was tried with it, which is scarcely adequate in so important a question.

"(3) Von Wiesner states that from all the human cases whose material he was able to avail himself of (he does not say how many) he succeeded in growing this organism. Apart from the fact that other investigators have not had a similarly successful experience, he nowhere states that the organism was found in the microscopical preparations of the cases concerned, nor does V. Economo mention his finding such an organism. We are apparently faced with the problem of an organism as definite as a diplostreptococcus not recognizable

[29] Wilson, S. A. K., Epidemic Encephalitis: Lancet, London, ii 7, 1918.

microscopically in nervous tissues, but, nevertheless, culturable from them. In view of the unsatisfactory nature of Von Wiesner's conclusions, the question whether this diplostreptococcus is the specific cause of the disease must be left open; the negative bacteriological findings in the tissues in my two fatal cases militate against the acceptance of the somewhat summary statement in Von Wiesner's communication."

Summary.

1. Clinically the disease presents a series of symptoms which are found in no other affection.

2. The lack of positive epidemiological data renders the determination of the length of an incubation period impossible.

3. The clinical course of the disease may be divided into three stages: A prodromal period with fatigue, lethargy, headache, giddiness, and disturbances of vision; the stage of acute manifestations, with vomiting, fever, paralysis of certain cranial nerves, changes in tendon reflexes, alterations in speech, marked general weakness, and, in the majority of cases, coma of varying intensity; and the period of convalescence, which varies. In some cases recovery is complete within ten days or two weeks after the subsidence of the acute symptoms. In other cases, however, convalescence is prolonged and is accompanied by changes in the mental state, definite loss of function of certain muscles, and obstinate palsies of the cranial nerves.

4. There was a distinct outbreak of the disease in the United States during the latter part of 1918 and the early part of 1919. Beginning with the first case in the city of New York in September, 1918, there was a gradual increase in the monthly incidence up to and including March, 1919, during which month 61 cases occurred. This was followed by a sharp break with only 12 cases in April and 5 in May.

5. The age distribution of the cases in epidemic encephalitis is entirely different from that in poliomyelitis, and is, it is believed, in itself alone to be sufficient grounds for the belief that the two diseases are separate and distinct affections.

6. The appearance of epidemic encephalitis in epidemic form has, with the exception of the cases reported by V. Economo, apparently always been preceded by an epidemic outbreak of influenza. This apparent relation between the two diseases remains as yet unsolved, and consequently, therefore, leaves a field for considerable discussion. Of the 122 cases of epidemic encephalitis on which definite data were obtainable, only 56 cases, or 46 per cent, gave a history of having had a preceding attack of influenza; whereas in 66 cases, or 54 per cent, the history of a recognized attack of influenza was negative. As shown in a previous section of these studies, this influenza attack rate is higher in the group of persons having had epidemic encephalitis than in the general population. The question naturally arises, "Why?" In seeking a solution to this

problem two lines of thought present themselves. First: Believing that epidemic encephalitis is a disease unto itself, may not this difference be due to the fact that those persons who have had influenza suffer a certain lowering of vitality, immunity, or resistance, which would render them more susceptible to the invasion of the causative agent of epidemic encephalitis when exposed to such a factor? If this be so it would account for the difference in the attack rate above mentioned. Second: If, however, the belief that epidemic encephalitis is a distinct disease is erroneous, may it not be possible that those cases classified as having had a previous attack of influenza are really recurrent invasions of the same person with the causative agent of influenza, whatever this agent may be, the second invasion involving or invading the central nervous system? An invasion of the central nervous system direct as a primary attack by this same agent, if such a thing be possible, would account for those cases which give no history of a previous attack of influenza. In the absence of definite positive laboratory findings in connection with the etiology of epidemic encephalitis, this thought is merely offered as a possibility.

7. Sex distribution shows 60 per cent of the cases males and 40 per cent females; whereas in influenza the attack rate for males and females is about equal. In the cases of epidemic encephalitis without a previous attack of influenza, the ratio of males to females is 1 to 1. In those cases having had a previous attack of influenza, however, the ratio of males to females is 2.5 to 1.

8. Onset was gradual in 71 per cent of cases and sudden in 29 per cent. The case fatality rate, however, was 60 per cent in the cases with sudden onset and 22 per cent in the cases where the onset was gradual.

9. Lumbar puncture and subsequent examination of the spinal fluid, while revealing very little of a positive nature, should be done in all cases where it is possible, as it is by this means that other conditions which might be confused with epidemic encephalitis may be eliminated to almost a certainty.

10. Blood examinations reveal very little data which may be used for diagnostic purposes.

11. As for communicability, approximately 900 persons were exposed in the immediate families of the cases reported in the United States, and among this number no secondary case occurred so far as reports and inquiries show.

12. The case fatality rate was 29 per cent.

13. The results of animal innoculation with brain material from two fatal cases in connection with these studies were negative. The fact must be borne in mind, however, that the brain material used had been retained in 50 per cent sterile glycerine for a period of six months prior to the inoculation.